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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/532,297	08/24/2005	Joseph Alexander Lasky	ON/4-32744A	1063

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EXAMINER	
THOMAS, TIMOTHY P	
ART UNIT	PAPER NUMBER
1628	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/532,297	LASKY, JOSEPH ALEXANDER	
	Examiner	Art Unit	
	TIMOTHY P. THOMAS	1628	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 January 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,5,7,10 and 11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,5,7,10 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments

1. Applicants' arguments, filed 1/19/2010, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

2. Applicant's arguments with respect to the scope of enablement rejection have been fully considered but they are not persuasive:

Claims 10, 2, 5, 7 and 11 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating pulmonary hypertension in the sense of the meaning of reduction of pulmonary hypertension in individuals with pulmonary hypertension, does not reasonably provide enablement for treating individuals in the sense of the meaning of prophylactic treatment.

The rejection is maintained for the reasons of record.

Applicant argues that all that is required for "prophylactic" treatment is for the compound to prevent the onset or recurrence of some episodes of pulmonary hypertension. While that may be one embodiment within the scope of "prophylactic" treatment, MPEP 2106 (II) (C) indicates:

> USPTO personnel are to give claims their broadest reasonable interpretation in light of the supporting disclosure. *In re Morris*, 127 F.3d 1048, 1054-55, 44 USPQ2d 1023, 1027-28 (Fed. Cir. 1997).... See also *In re Zletz*, 893 F.2d

> 319, 321-22, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989) ("During patent examination the pending claims must be interpreted as broadly as their terms reasonably allow.... The reason is simply that during patent prosecution when claims can be amended, ambiguities should be recognized, scope and breadth of language explored, and clarification imposed....

Applicant argues that there is no reasonable basis to interpret the present specification as requiring for the prophylactic use of the compound to prevent all pulmonary hypertension in the patent; that even the definition of "prevent" offered by the Examiner does not require no episodes to occur; that the only requirement is the prevention of some episodes that would have occurred without the treatment.

This is not persuasive. The broadest reasonable interpretation of the claim language "treating" has the meaning of curative treatment and prophylactic treatment; the term "prophylactic" means the prevention of the onset or recurrence of pulmonary hypertension (see instant specification, p. 5, lines 8-12). The record indicates that "prevent" has the meaning of "to keep from happening or existing" (Merriam-Webster online definition of Prevent; http://www.merriam-webster.com/dictionary/prevent; accessed 10/14/2009). It is clear from the disclosed definitions that treating has embodiments of preventing onset of pulmonary hypertension and preventing the recurrence of pulmonary hypertension. Taken with the definition of "prevent", the broadest reasonable interpretation of the claims includes prevention of pulmonary hypertension' i.e., to keep pulmonary hypertension from happening and existing, by the administration of the claimed drug therapy, irrespective of the etiology.

Applicant argues the specification clearly teaches that the present compound has utility as a prophylactic treatment for preventing some episodes of pulmonary hypertension; that the present specification contains data demonstrating that the present compound reduced hypoxic-induced pulmonary hypertension; that in view of such disclosure, it is the Examiner's burden to explain why they doubt the truth or accuracy of statements and made in the disclosure and to back up such assertions with acceptable evidence or reasoning; that the Examiner attempts to meet this burden with conclusory statements relating to the poor prognosis and need for better drugs, but this does not provide a rational basis to doubt the present applications' clear teaching.

This is not persuasive; a rationale has been presented; the Wands factors have been analyzed and discussed (see 4/1/2008 Office Action, Item 5, pp. 3-5); the record indicates with respect to the state of the art and the unpredictability demonstrated in the art:

> Fukumoto, et al. ("Recent Progress in the Treatment of Pulmonary Arterial Hypertension: Expectation for Rho-Kinase Inhibitors"; 2007; Tohoku Journal of Experimental Medicine; 211: 309-320) teaches pulmonary arterial hypertension (PAH) is a disease with poor prognosis characterized by progressive elevation of pulmonary arterial pressure and vascular resistance due to pulmonary hyperconstriction and remodeling; the precise mechanism still remains to be elucidated (abstract); although anticoagulant agents, vasodilators and lung transplantation are currently used in the treatment of PAH, more effective treatment needs to be developed (abstract; p. 317, right 3rd paragraph); the WHO

classification of pulmonary hypertension is divided into 5 categories with multiple disease listings in each of these categories (p. 310, Table 1), and Figure 1 (p. 312) shows "unknown triggers at the top of the illustration of pathophysiological components contributing to the development of pulmonary hypertension. These characteristics demonstrate the diversity and complexity of pulmonary hypertension as a group of diseases, and suggest that a treatment to cure and prevent the diseases would be unpredictable

With regard to the guidance provided by the specification, the record indicates:

The specification has provided guidance for an 80% reduction of pulmonary hypertension in rats that had been exposed to hypobaric-hypoxic conditions. However, the specification does not provide examples nor reasoning that would support the claim to prevent or cure pulmonary hypertension.

With regard to the quantity of experimentation required, the record indicates:

Considering the state of the art as discussed by the references above, particularly with regards to the many related diseases that are considered pulmonary hypertension, the current poor prognosis in patients, the precise mechanism by which pulmonary arterial pressure is elevated is unknown and the disease is initiated by unknown triggers and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

While it is true that conclusions have been reached and articulated, a rationale for enabling "prevention" would likely require knowledge of each of the mechanism(s) by which a disease such as pulmonary hypertension occurs, than such knowledge might be addressed by drug therapy; alternately, "prevention" could be demonstrated by experimental evidence showing demonstrating prevention of pulmonary hypertension occurs. The disclosed reduction in pulmonary hypertension is enabling for other embodiments within the scope of treatment, but an 80% reduction does not demonstrate full remission (which might support curative treatment) and is not sufficient to demonstrate that pulmonary hypertension can be kept from occurring (an 80% reduction leads to an expectation that pulmonary hypertension will still occur, but to a lesser extent or delayed disease progression, in contrast to prevention). When the Wands factors are weighed, the conclusion is reached that the prevention embodiment, within the scope of treating, is unlikely to be efficacious to keep pulmonary hypertension from occurring, especially in light of the recognition in the art that current therapies need improvement, and that there are causes of pulmonary hypertension that are currently not known, and that some pulmonary hypertension is expected based on the data disclosed in the specification; i.e., it is not likely that every (or even some) unknown trigger of pulmonary hypertension will be stopped by the claimed drug therapy. The prevention embodiment is maintained to require undue experimentation to practice commensurate in scope to the claims.

3. Applicant's arguments with respect to the rejection under 35 USC 103 have been fully considered but they are not persuasive:

Claims 10, 2, 5, 7 and 11 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Goncharova, et al. ("PI3K is required for proliferation and migration of human pulmonary vascular smooth muscle cells"; 2002 Mar 8; Am. J. Physiol. Lung Cell. Mol. Physiol.; 283: L354-L363; cited in a prior Office Action); Tanabe, et al. ("Mechanical stretch augments PDGF receptor β expression and protein tyrosine phosphorylation in pulmonary artery tissue and smooth muscle cells"; 2000; Molecular and Cellular Biochemistry; 215: 103-113; cited in a prior Office Action); Zimmermann, et al. (WO 99/03854 A1; 1999; IDS 4/21/2005 reference AM); and Dingli, et al. ("Unexplained Pulmonary Hypertension in Chronic Myeloproliferative Disorders"; 2001; Chest; 120 (3): 801-808; cited in a prior Office Action).

The rejection is maintained for the reasons of record.

Applicant argues that the language used in discussing the rejection; i.e., that PI3K-dependent human PVSM cell motility "may" offer a potential target in blocking development of hypertension; that the references "imply" that the relationship that exists between PDGFR activity and pulmonary hypertension, merely suggests a field for further experimentation, that nothing in such a disclosure would lead to a reasonable expectation of success.

The record indicates, in part (see 4/1/2008 Office Action, Item 7, pp. 6-7):

> Goncharova teaches human vascular smooth muscle cell proliferation and migration contribute to vascular remodeling in pulmonary hypertension and atherosclerosis; that stimulation of human pulmonary vascular smooth muscle (PVSM) with platelet derived growth factor (PDGF) induced PI3K-dependent

activation of Akt, p70 S6 kinase and ribosomal protein S6; and that PDGF-induced proliferation and migration was inhibited by LY-294002 (a kinase inhibitor; abstract); PDGF appears to be the most potent activator of the PI3K signaling pathway in many cell types (p. L360, last paragraph); regulation of cell proliferation and motility is a critical step in vascular remodeling, and suggests that targeting PI3K-dependent human PVSM cell motility and proliferation may offer a potential target in blocking development of lesions in atherosclerosis and hypertension (p. L362, last paragraph).

Tanabe teaches mechanical stretch of pulmonary artery tissue identified tyrosine phosphorylation proteins that respond to mechanical stress, which included p55 as one of two proteins preferentially phosphorylated by stretch in endothelial cells, corresponding to PDGF receptor β; significant increase in RNA level for PDGF-Rβ was observed in the pulmonary artery of rats with induced pulmonary hypertension, suggesting that stretch-induced overexpression of cell-surface PDGF-Rβ as well as augmentation of tyrosine phosphorylation of proteins might be involved in the mechanotransduction of pulmonary artery (abstract); mechanical stimulus such as stretch induces several responses including smooth muscle contraction, proliferation and apoptosis (p. 103, 1st paragraph); and an inhibitor of tyrosine kinase specifically suppressed the pressure-induced contraction of rat cerebral artery (p. 104, 2nd paragraph).

Blocking PI3K-dependent human PVSM cell motility is expected from inhibition of PDGF; and reduction of PDGF levels would be expected to benefit in therapy of

pulmonary hypertension, based on these references. Taking into account that Zimmerman clearly indicates imatinib and imatinib mesylate are active inhibitors of PDGF, and are useful in diseases where vascular smooth-muscle cell migration and proliferation where PDGR and PDGF-R play a role (see 4/1/2008 Office Action, Item 7, pp. 7), the administration of the claimed compounds would have been expected to provide a benefit in therapy of pulmonary hypertension. There would have been a reasonable expectation of success based on the teachings of these references, taken in combination.

Applicant further argues that the expectation of rapamycin and imatinib as equivalent for the treatment for pulmonary hypertension only provides a basis for experiment, but gives no reasonable expectation of success. The substitution of one compound for another, with the same properties is a rationale consistent with KSR Exemplary Rationale (B): Simple substitution of one known element for another to obtain predictable results (see MPEP 2141 (II) (C)). With respect to the level of expectation of success, MPEP 2143 (B) (Example 2) indicates that "obviousness does not require absolute predictability of success". There is a reasonable expectation based on the references that the claimed compounds would provide a benefit in treatment of pulmonary hypertension.

Applicant argues that Tanabe taken with Goncharove would lead to try to control pulmonary hypertension with S6K1 inhibitors, but not with PDGFR inhibitors. This is not persuasive; such a rationale has been presented above and in the record.

Applicant argues that Tanabe merely reports experiments that suggest a correlation between PDGF-Rβ in vasculature hypertensive diseases, but such a report does not suggest that inhibition of PDGFR is an appropriate treatment for the condition. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The claimed compound would have been expected to provide a benefit for treatment of pulmonary hypertension at the time of the instant invention, based on the combination of references.

Conclusion

4. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TIMOTHY P. THOMAS whose telephone number is (571)272-8994. The examiner can normally be reached on Monday-Thursday 6:30 a.m. - 5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Timothy P Thomas/
Examiner, Art Unit 1628

/Brandon J Fetterolf/
Primary Examiner, Art Unit 1642